Peer Review File

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Reviewer A

This was a retrospective study aimed to evaluate the use of adjunctive perampanel in people with Dravet syndrome.
The study addressed a clinically meaningful topic. There are, however, some issues that need to be addressed.

Author response:
Dear reviewer, we highly appreciate your remarks.

It would be fine to comment about the currently available evidence on recently developed antiseizure medications for Dravet syndrome and comment about the positioning of perampanel in regard of these new compounds (Ref. Pharmacotherapy for Dravet Syndrome: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Drugs. 2023).

Author response:
Dear reviewer, thank you for your valuable comment. Kindly note that we examined and analyzed the article your referenced (i.e., Pharmacotherapy for Dravet Syndrome: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Drugs. 2023) and added a new paragraph in the introduction section (**Page 5-6, lines 61-70**), in regards to your point about the positioning of perampanel, we refer your kind attention to **page 6, lines 82-86** in which we thoroughly discussed the most recent evidence on the use of perampanel. We hope this adjustment satisfies your comment.

We added new paragraphs on **page 5-6, lines 63-73.**

Perampanel has been shown to be a valid option for the treatment of seizures associated with another developmental and epileptic encephalopathy as Lennox-Gastaut syndrome (Ref. Long-term effectiveness of add-on perampanel in patients with Lennox-Gastaut syndrome: A multicenter retrospective study. Epilepsia. 2023). It would be fine to expand on this evidence and highlight the broad-spectrum activity of perampanel across seizure types and syndromes.

Author response:

Dear reviewer, thank you for your valuable comment. Kindly note that we further elaborated on the role of perampanel among Lennox-Gastaut syndrome and kept the segment on **page 6, lines 76-80** exclusively on Lennox-Gastaut syndrome due to its genetic nature and similarity to Dravet syndrome in being on the genetic epilepsy syndromes. In the subsequent paragraph we discussed the role of perampanel among other forms of seizure in general.

We added new paragraphs on **page 6, lines 78-82.**

We thank you for your valuable comments and hope our answers satisfies you. We believe that these comments and the adjustments we made enhanced the quality of the paper and we look forward to any further comments if needed.

Reviewer B

This submission is an observational study addressed to calibrate the efficacy and tolerability of the AMPA antagonist perampanel as antiepileptic therapy in children affected by Dravet syndrome. Perampanel has been recently approved for the treatment of seizuring activity, including pediatric epilepsy, so it is currently being used in DS patients. The idea of this study is interesting, but there are some important questions that require to be better justified or explained. The major problems are listed below:

1. An important concern derives from the way used by authors to select the patients that are included in this observational study. The information in this sense is limited despite this is critical aspect due to the risk of potential bias. Authors must be more precise in this question.

Author response:
Dear reviewer, thank you for your valuable comment. Kindly note that we added the word "all" to **page 6, line 92**, to emphasize that after we reviewed the medical records of all of our pediatric patients who were diagnosed with Dravet syndrome and included all those who were given perampanel or they are currently on the medication as described in **page 7, line 93**. We also elaborated on the search time frame and included a paragraph on **page 6-7, lines 93-94**. Furthermore, the sampling technique was in accordance to Julious (2005) which recommend a minimum of 12 participants when testing a single treatment arm. However, we did not discuss the sampling technique since we included our entire population rather than drawing a sample out of it. If this's needed, we may still add this information. Moreover, you may consider the number of

participants is still small but we note that the treatment has been only recently approved and made available in clinical practice. Despite this, according to the extent of our knowledge, we still reported the largest cohort of Dravet syndrome patients. We hope this satisfies your comment and we would be happy to address any further adjustments.

We added a new word on **page 6, line 92** and paragraph on **page 6-7, lines 93-94.**

2. The Introduction should include more information on the different medications used for DS patients, their efficacy, their problems, as well as the recent therapies arrived for these patients as cannabidiol and fenfluramine.

Author response:
Dear reviewer, thank you for your valuable comment. Kindly note that we added this information and tailored it with the comment of another reviewer who suggested a very similar modification. The updated introduction now thoroughly discusses the points you mentioned and included further elaboration on the efficacy and limitations of perampanel in Dravet syndrome as well as recent findings for other antiseizure medications and its efficacy and adverse events in patients with Dravet syndrome. These medications also include your suggestion (i.e., cannabidiol and fenfluramine). The new paragraphs are located in **page 5-6, lines 63-73** and **page 6, lines 78-82**.

3. Materials and Methods: Authors included a subsection on the different statistical analyses conducted, but the tables and figures did not show any data that have required this type of analysis. The data presented in the text (Results section) are expressed simply as percentages or means ± SD, but there was not any comparison between groups or variables, so it is not clear why when they used ANOVA, Pearson's chi-square, Mann-Whitney or Kaplan-Meier. This should be corrected.

Author response:
Dear reviewer, thank you for your valuable comment. The statistical analysis section was reviewed and adjusted accordingly, with the addition of the specific relation that was done following each statistical tests mentioned.

We updated the statistical analysis section on **page 8, lines 116-118.**

4. The new therapies with fenfluramine or cannabidiol should be also indicated in figures 1 and 2.

Author response:

Dear reviewer, thank you for your valuable comment, kindly note that figure 1 has been updated to include fenfluramine and cannabidiol. However, in figure 2, we reported the most commonly used ASMs among our patients, we did not report the use of fenfluramine and cannabidiol because these medications are still not available in our institute.

We added a new paragraph in **page 25, lines 390-391.**

We thank you for your valuable comments and hope our answers satisfies you. We believe that these comments and the adjustments we made enhanced the quality of the paper and we look forward to any further comments if needed.

Reviewer C

(i) it would be useful to have some information in the introduction about which ASMs can be effective in Dravet, also including information about whether dietary therapies such as ketogenic can be effective

Author response:
Dear reviewer, thank you for your valuable comment. In regards to the first part of your comment, kindly note that we elaborated on other ASMs which was also suggested by the other reviewers and added new paragraphs on **page 5-6, lines 63-73** and **page 6, lines 78-82** discussing the use of other ASMs as well as PER effect on other genetic epilepsy syndromes. We did our best to accommodate your comment with the other queries. However, regarding the role of ketogenic diet, kindly note that we added a new paragraph on **page 5, lines 61-63**.

We added a new word on **page 5, lines 61-63.**

(ii) Introduction: mention of the commonly described side effects of perampanel

Author response:
Dear reviewer, thank you for your valuable comment. Kindly note that a new paragraph on the side effects of perampanel has been added on **page 6, lines 84-85**.

We added a paragraph on **page 6, lines 84-85.**

(iii) in section 3.1, age of patent is age at review? Better given as medan (range)

Author response:
Dear reviewer, thank you for your valuable comment. As per your request, the age at review in both the results and the table was displayed by median rather than mean. We also followed the journal guidelines in reporting the median and ranges.

We added more details on **page 8, lines 126-130**.

(iv) similarly give age at PER initation as median (range)

Author response:
Dear reviewer, thank you for your valuable comment. As per your request, the age at PER initiation in both the results and the table was displayed by median rather than mean.

We added more details on **page 8, lines 126-130**.
We added more details on **page 21, line 380 (table 2 – median and IQR added.)**.

(v) ages should all be given as either years+months, months, or fractional years (e.g., 4.6 years), rather than whole years >1 and months <1.

Author response:
Dear reviewer, thank you for your valuable comment. We used the (years+months) in displaying data especially since data such as the age of the seizure onset was in month and the ages of PER initiation are in years. For easier reading we didn't uniform all ages into months as some ages, for example patient 2 in table 1 would be 108 months old when PER is initiated. However, our current reporting form is easier to read and follows standard reporting in other articles. Regarding the whole years point (years >1 and months <1), we only adopted such style in the 3.4 bivariate section in the results which we needed to group our patients into two groups to assess the efficacy of PER when administered earlier that the chosen cut off point. However, if we misunderstood your request or you consider further modifications we would happily do so.

(vi) it would also be useful to include in Table 1 length of time on PER

Author response:
Dear reviewer, thank you for your comment. Kindly note that this information is present in the text in **page 9, lines 143-144** for the patients as a whole as we did not any clinical significance to report the information individually. We may add this to the limitation

section.

(vii) weight = weight at follow up? As the age of all these patients, it would make more sense to calculate a Z-score using WHO 2006 Growth Charts

Author response:
Dear reviewer, thank you for your comment. Patient weight was not available in our medical record for the follow up given that the follow up periods varied significantly among the patients. It is also irrelevant in this case as we explained in your query (ix) that PER was approved for its use as an mg per day rather than in relationship to the weight. We may also add this to the limitation section.

(viii) I am not an expert on genetics or classifaction of epilepsy syndromes but I believe that PCDH19-related epilepsy is distinct from Dravet so this patient should be removed from the dataset, or at least acknowledged that not all patients are Dravet.

Author response:
Dear reviewer, thank you for your valuable comment. As you know DS constitute several genes with SCN1A representing 80% of genetic etiology for this syndrome. In recent studies, the remaining percentages had been researched and showed several genes to be linked to DS including a mutation in the PCDH19 gene. In one study, it was found that up to 25% of patients with SCN1A-negative DS patients had PCDH19 mutations. It also suggested that PCDH19 can account to up to 5% of all DS mutations. So, a correlation between PCDH19 and DS should be established genetically using advanced genetic testing as in our case and the correlation of clinical manifestations that are well-established to DS in which our patient presented with. For that, our genetic report and clinical judgment included this patient as DS patient.

References:

1- Marini C, Scheffer IE, Nabbout R, Suls A, De Jonghe P, Zara F, Guerrini R. The genetics of Dravet syndrome. Epilepsia. 2011 Apr;52 Suppl 2:24-9. doi: 10.1111/j.1528-1167.2011.02997.x. PMID: 21463275.
2- Depienne C, Bouteiller D, Keren B, Cheuret E, Poirier K, Trouillard O, Benyahia B, Quelin C, Carpentier W, Julia S, Afenjar A, Gautier A, Rivier F, Meyer S, Berquin P, Hlias M, Py I, Rivera S, Bahi-Buisson N, Gourfinkel-An I, Cazeneuve C, Ruberg M, Brice A, Nabbout R, Leguern E. (2009b) Sporadic infantile epileptic encephalopathy caused by mutations in PCDH19 resembles Dravet syndrome but mainly affects females. PLoS Genet 5:e1000381. Epub 2009 Feb 13.

(ix) given the age range it would be useful to express doses as mg/kg

Author response:

Dear reviewer, thank you for your valuable comment. Perampanel was approved by the FDA in the doses of 2,4,6,8,10,12 mg per day. It was not like other standard medications that were approved and advised to be used on an mg/kg. Therefore, we reported it as per the FDA's approval. Another example is table 3 in this article (The efficacy of perampanel in young children with drug-resistant epilepsy) which displays used doses in mg only.

Table 3
Demographic characteristics of TSC patients treated with perampanel.

Patient	Age (years/Sex)	Mutations	Seizure types	Other comorbidities	Dose (mg)	Concomitant AEDs	Treatment response	Reference
1	14 / F	Not mentioned			4	OXC, VGB, CBZ	≥ 50 %seizure reduction in 5 months	[13]
2	16 / F	Not mentioned	Focal aware		12	SCB, LEV	No benefit	[14]
3	3 / M	TSC1	Epileptic spasms, tonic	ID, cardiac tumor, WPW syndrome	2	VGB, LEV, CBZ, VPA	Aggravation (increased tonic seizure)	Present series
4	1 / F	TSC2	Focal tonic	DD	2	OXC, LEV, sirolimus	No benefit	
5	1 / M	TSC2	Epileptic spasms, tonic		2	VGB, VPA, CBZ, TPM	> 50 % reduction in 6 months and seizure free in 1 year	
6	3 / M	TSC2	Gelastic, atonic	ASD, ID, cardiac tumor	4	VGB, VPA, TPM, everolimus	> 50 % reduction in 6 months and 1 year	
7	4 / F	TSC2	FLE, GTCs	left hemiparesis, CHD	3	VGB, VPA, LEV, LMT, ZNS	> 50 % reduction in 6 months and 1 year	
8	6 / F	TSC2	TLE, absence	ID	2	VGB, VPA, LEV, ZNS	> 50 % reduction in 6 months and 1 year	

*AEDs: Antiepileptic drugs; ASD: autism spectrum disorder; CBZ: Clobazam; CHD: congenital heart disease; DD: developmental delay; FLE: Frontal lobe epilepsy; GTCs: Generalized tonic-clonic seizures; ID: intellectual disability; LMT: Lamotrigine; LEV: Levetiracetam; NF: neurofibromatosis; OXC: Oxcarbazepine; PER: Perampanel; SCB: sodium channel blocker; TLE: Temporal lobe epilepsy; TPM: Topiramate; TSC: tuberous sclerosis; VPA: Valproic acid; VGB: Vigabatrin; ZNS: Zonisamide.

Seizure: European Journal of Epilepsy 75 (2020) 82–86

Link for FDA instructions:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202834s011lbl.pdf

Discard any unused FYCOMPA oral suspension remaining 90 days after first opening the bottle.

3 DOSAGE FORMS AND STRENGTHS

Tablets

- 2 mg tablets: orange, round, debossed with "2" on one side and "Є 275" on the other.
- 4 mg tablets: red, round, debossed with "4" on one side and "Є 277" on the other.
- 6 mg tablets: pink, round, debossed with "6" on one side and "Є 294" on the other.
- 8 mg tablets: purple, round, debossed with "8" on one side and "Є 295" on the other.
- 10 mg tablets: green, round, debossed with "10" on one side and "Є 296" on the other.
- 12 mg tablets: blue, round, debossed with "12" on one side and "Є 297" on the other.

Oral Suspension

0.5 mg/mL white to off-white opaque liquid suspension for oral administration.

4 CONTRAINDICATIONS

None.

(x) what was the reason for cessation of PER in the 13 patients who failed, was it always lack of efficacy, or was it for other reasons (e.g., side effects). Also, according to the table 14/18 patients, not 13 seem to have stopped PER.

Author response:
Dear reviewer, thank you for your valuable comment. The cessation reasons varied among the patients. However, they were mainly due to the families' preference. In most cases, the new onset of some side effects including drowsiness was worrying to the families and made them request the cessation of the medication and the replacement of PER with another ASM despite showing good efficacy. Others requested the cessation due to the lack of improvement so they requested other options that could quickly reduce seizure frequency.

(xi) section 3.4 The authors have erxamined the relationship between age and PER effectiveness. however, it is not clear which age is being used here - age at review, or age at initation of PER? It only makes sense to analyse by age at initiatiion of PER. This may necessitate rewriting the results, discussion, conclusions and the abstract

Author response:
Dear reviewer, thank you for your valuable comment. The examined relationship was indeed between the age of PER initiation and PER efficacy as this is the only clinically relevant information. Also, during the age of review, some patients had ceased the medication so indeed it makes no sense to measure efficacy at the age of review.

(x) discussion could be shorter and more focused

Author response:
Dear reviewer, thank you for your valuable comment. Kindly note that we shortened many paragraphs in the discussion and they were as follows:

We shortened the paragraph in **page 10 lines 172**, **page 10-11 lines 178-182**, deleted **page 11-12 lines 199-205**. Deleted **page 12 lines 202-209**, and shortened paragraph on **page 12 lines 207-213**.

We believe that the discussion is more concise and focused now and we'd be happy to address further concerns.

We shortened the paragraph in **page 10 lines 172**, **page 10-11 lines 178-182**.
We deleted paragraph in **page 11-12 lines 199-205**.
We deleted paragraph in **page 12 lines 202-209**.
We shortened the paragraph in **page 12 lines 207-213**.

(xi) The conclusions of both the abstract and the discussion state "evidence of promising therapeutic potentials for PER among some patients with DS" which is not incorrect, bit in order to be more balanced, the fact that 14/18 patients had stopped PER needs to be stated

Author response:
Dear reviewer, thank you for your valuable comment. PER did indeed show good efficacy and as explained in your query (x). The medication cessation causes included mainly family's preference. Therefore, we added this information to the abstract in **page 2 lines 35-36** and further details were discussed in the discussion part.

We a new paragraph on **page 2 lines 35-36**.

We thank you for your valuable comments and hope our answers satisfies you. We believe that these comments and the adjustments we made enhanced the quality of the paper and we look forward to any further comments if needed.